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Early loss of physiologic coherence: A bedside framework to anticipate sepsis deterioration

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Despite major advances in critical care, sepsis and septic shock continue to be identified primarily through the consequences of physiologic failure rather than through the mechanisms that initiate systemic deterioration. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) represented a conceptual advance by defining sepsis as life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. However, its operational criteria—organ dysfunction quantified by the SOFA score, vasopressor requirement, and lactate elevation—identify the syndrome only after systemic dysregulation has already translated into established organ injury. This temporal dissociation between physiologic collapse and clinical recognition remains a central limitation of contemporary sepsis care.

Importantly, Sepsis-3 was not designed to detect the earliest stages of physiologic instability. Its goal was to establish a prognostically meaningful construct once organ dysfunction is present. In this sense, Sepsis-3 defines what sepsis is, not when it begins. Recent updates such as SOFA-2 modernize variables and thresholds to reflect contemporary practice, but they remain consequence-based by design and were not intended to anticipate early physiologic failure [2]. The persistent challenge is therefore operational rather than conceptual: how to recognize, at the bedside and in real time, the transition from an adaptive host response to maladaptive systemic dysregulation before irreversible organ injury develops.

From a physiologic standpoint, sepsis is a dynamic and continuous process rather than a binary state. Early during infection, compensatory mechanisms preserve tissue perfusion and cellular metabolism through coordinated cardiovascular, microcirculatory, and autonomic responses. Increased sympathetic tone, microvascular recruitment, and metabolic flexibility allow the organism to meet increased energetic demands while maintaining organ function. As the inflammatory response progresses, endothelial injury, altered vasomotor regulation, microcirculatory heterogeneity, and mitochondrial dysfunction progressively erode this adaptive reserve [3,4]. Crucially, this deterioration does not initially manifest as hypotension, hyperlactatemia, or overt organ failure, but rather as a loss of coherence between macrocirculatory variables and tissue-level perfusion.

We propose that the earliest clinically actionable signal of sepsis deterioration is the loss of physiologic coherence, defined as the failure of integrated cardiovascular and metabolic regulation to maintain effective tissue perfusion despite apparently preserved systemic parameters. This loss precedes organ dysfunction and is detectable using simple bedside markers that reflect systemic regulation rather than isolated organ injury.

Clinically, early loss of physiologic coherence manifests as subtle but consistent abnormalities across multiple bedside domains. Prolonged capillary refill time (CRT), widening central-to-peripheral temperature gradients, declining urine output, and mild alterations in mental status often occur while blood pressure, oxygen saturation, and even lactate levels remain within accepted ranges. Similarly, an inappropriate tachycardic response—either disproportionate to fever or pain, or characterized by reduced heart rate variability—may signal early autonomic dysregulation. These findings should not be interpreted in isolation; rather, their convergence reflects the breakdown of coordinated physiologic control.

Endothelial dysfunction and microcirculatory derangements play a pivotal role in this process. In sepsis, impaired vasoreactivity and heterogeneous capillary flow lead to regional hypoperfusion despite preserved or increased global blood flow [3]. As a result, traditional macrocirculatory targets may normalize while tissue oxygen delivery remains inadequate. The concept of cardiovascular or hemodynamic coherence emphasizes this dissociation, highlighting that normalization of systemic variables does not guarantee restoration of effective tissue perfusion or cellular metabolism [5]. Loss of coherence therefore represents a failure of integration rather than failure of any single organ system.

Importantly, microcirculatory alterations do not follow a uniform pattern across all septic patients. The physiologic expression of sepsis is highly heterogeneous, and loss of coherence may emerge through different dominant mechanisms, including vasoplegia, relative hypovolemia, myocardial dysfunction, or altered autonomic regulation. Thus, impaired physiologic coherence should be understood as a convergent functional state resulting from diverse pathophysiologic trajectories rather than a single microcirculatory phenotype.

Septic shock represents the extreme end of this continuum. According to Sepsis-3, septic shock is defined by vasopressor dependence to

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maintain a mean arterial pressure ≥ 65 mmHg and elevated lactate levels despite adequate fluid resuscitation [1]. Although these criteria are strongly associated with mortality, they define shock through therapeutic interventions and biochemical consequences rather than through underlying mechanisms. Vasopressor use reflects a clinical decision influenced by timing, local practice patterns, and evolving resuscitation strategies, rather than a direct marker of pathophysiology [6].

The growing emphasis on early vasopressor initiation further challenges shock definitions anchored to treatment requirements. Early norepinephrine administration has been associated with improved outcomes and reduced fluid exposure, supporting its use before the development of overt hypotension [7]. Consequently, many patients experience significant circulatory and metabolic stress that rapidly resolves with early intervention and never fulfill formal septic shock criteria. Conversely, patients meeting identical criteria may exhibit fundamentally different hemodynamic profiles, including predominant hypovolemia, vasoplegia or myocardial depression [8], yet receive similar initial management. These discrepancies underscore the limitations of consequence-based definitions for guiding individualized therapy.

Lactate illustrates this limitation particularly well. Although widely used as a marker of tissue hypoperfusion, lactate elevation in sepsis reflects a complex interplay of adrenergic stimulation, altered pyruvate metabolism, regional flow redistribution, and impaired clearance, rather than anaerobic metabolism alone [9]. While lactate remains a powerful prognostic marker, it is an imprecise indicator of early perfusion failure. Normal lactate values do not exclude significant microcirculatory dysfunction, particularly during the early phases of sepsis [10].

In contrast, peripheral perfusion markers directly reflect tissue-level blood flow. CRT has emerged as a robust bedside indicator of systemic regulation and tissue perfusion. Observational studies have consistently associated prolonged CRT with increased mortality in septic patients [11]. More importantly, randomized trials have demonstrated that targeting CRT during early resuscitation is at least as effective as lactate-guided strategies and may reduce unnecessary fluid administration [12]. Recent data confirm that personalized, CRT-guided hemodynamic resuscitation improves outcomes in early septic shock [13], reinforcing the clinical relevance of perfusion-based assessment.

Beyond peripheral perfusion, simple arterial pressure–derived indices may further characterize circulatory incoherence. Low diastolic arterial pressure and an elevated diastolic shock index reflect impaired vascular tone and altered ventriculo-arterial interaction, identifying patients with predominant vasoplegia who may benefit from earlier vasopressor support [14]. When integrated with perfusion markers, these variables help link bedside observations to underlying cardiovascular mechanisms.

These bedside findings should not be interpreted as fixed therapeutic targets but rather as early physiologic warning signals indicating increasing vulnerability of systemic regulation. Their primary clinical value lies in prompting intensified reassessment, closer monitoring, and mechanism-oriented optimization before overt organ dysfunction develops, rather than triggering uniform interventions in isolation.

Building on these principles, we propose a physiology-centered bedside framework structured around three overlapping domains of systemic regulation (Fig. 1):

(1) Early loss of homeostatic control, identified by abnormal CRT, temperature gradients, urine output, and mental status;
(2) Circulatory incoherence, reflected by inappropriate tachycardia, low diastolic arterial pressure, widened pulse pressure, or an elevated diastolic shock index;
(3) Metabolic and cellular stress, evidenced by rising lactate levels and widening veno-arterial CO_2 gaps.

Progression through these domains marks the transition from adaptive response to maladaptive physiology. This progression is dynamic and heterogeneous, emphasizing the need for repeated bedside reassessment rather than reliance on static thresholds. Loss of physiologic coherence represents the point at which compensatory mechanisms can no longer sustain effective perfusion and metabolic homeostasis, even if conventional diagnostic criteria are not yet fulfilled.

This framework does not aim to redefine sepsis or septic shock, nor does it challenge the conceptual or prognostic validity of Sepsis-3. Rather, it complements existing definitions by offering an operational lens through which clinicians can recognize the moment of physiologic inflection, when early, mechanism-guided intervention may still prevent irreversible organ injury. Its reliance on bedside physiology ensures applicability across diverse clinical environments, including low-resource settings where advanced monitoring may be unavailable.

In this context, the proposed framework may help identify a transitional physiologic stage preceding established organ dysfunction,

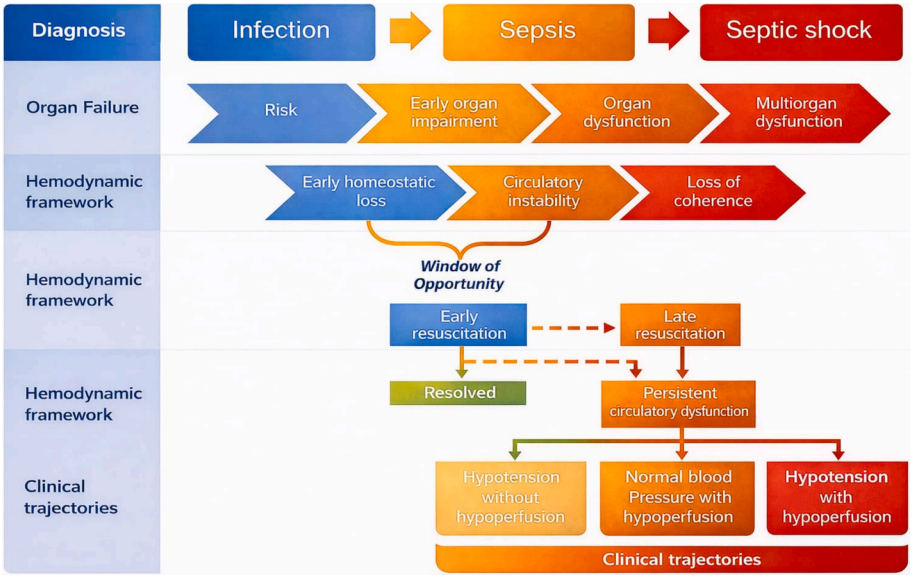

Fig. 1. Conceptual schematic Integrated representation of the transition from infection to shock, relating organ deterioration and progressive hemodynamic disarray to distinct clinical pathways shaped by early versus delayed resuscitation.

conceptually aligned with emerging discussions describing a potential "pre-sepsis" phase characterized by early systemic dysregulation before fulfillment of Sepsis-3 criteria [15], reinforcing the view of sepsis as a continuous process rather than an abrupt diagnostic transition. Importantly, this perspective does not propose a new diagnostic category but rather provides a bedside physiologic interpretation of this transitional state within the existing Sepsis-3 paradigm.

In conclusion, sepsis remains a syndrome defined physiologically but diagnosed operationally by its downstream consequences. The loss of physiologic coherence represents a unifying, bedside-detectable signal of impending systemic failure that precedes organ dysfunction and shock. Integrating this concept into early clinical assessment may help bridge the persistent gap between physiologic understanding and timely recognition, enabling earlier, individualized and physiology-guided intervention in patients with sepsis.

Authors' contribution

CS conceptualized and wrote the original draft, then both CS and EK edited and rewritten the manuscript. All authors read and approved the final manuscript.

Include clinical trial registration information

NA.

CRediT authorship contribution statement

Carlos Sanchez E.: Writing – review & editing, Writing – original draft, Visualization, Investigation, Conceptualization. **Eduardo Kattan:** Writing – review & editing, Validation, Methodology, Investigation.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

NA.

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